MMJ K4

July 28, 1942

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Dear Dr. Hershey:

First of all, I want to say that I have given your three carefully thought-out papers in the December Journal of Immunology a great deal of study, for they deserve it. I have not always been able, however, to follow your meaning or some of the seemingly vast leaps you toss off nonchalantly here and there. Although I have even called together a fairly large group of those here who should have been interested, in the hope of a stimulating evening's discussion I shall have to carry it on with you alone, for my younger friends, repeatedly thrown off, lacked the patience to return to your papers again. I do not say this by way of criticism, as Gibbs met much the same fate, but merely to urge you to heed the last sentence of your third paper and simplify matters a bit.

I have many questions and comments, but freely admit some may be due to a lack of understanding in spite of many attempts:

Page 457 - You say no assumptions need be made as to A valence, but you promptly make it >1. I agree, of course, but your wording makes you seem inconsistent. Also, why should the equilibrum be more influenced by G surfaces than by those of A? Why does it help to assume "initial reactions" before aggregations begin? Especially when your list of them is incomplete ($GA + G$ and $GA_2 + G$, for instance)? This omission seems to me fundamental and a fatal weakness of your treatment right at the start. This is aggregation, as well as "initial reaction." However, let us go on, anyway:

Page 460 - It is difficult for me to see how even a fictitious x can be 1 at the equivalence point, in view of experimentally established ratios.

Page 461 - Kabat's and my reagglutination experiment is an earlier and perhaps more decisive indication than

Duncan's. Why will specific and non-specific forces necessarily oppose?

Page 464 - According to our view this conclusion occasions no surprise.

Page 469 - If $r > (g-1)$ how can it ultimately be $< (g-1)$? I'm sure some people quit here.

Page 474 - Your equivalence zone ~~and~~ r values do not seem to be in accord with fact. How can an "equivalence point" be in the "inhibition zone?"

Page 475 - Do you mean that maximum A precipitation does <u>not</u> occur either in the equivalence zone or at slight G excess?

Page 479 - The Ramon optinum is certainly not in the xsA region in the Toxin - A system.

Page 480-2 - Your difficulties lead to the question I've often asked myself: can anything of real scientific value come out of these interminable constant proportion arguments? Our recalculation of Taylor and Adair's experiments show there is no fundamental theoretical difference between the constant G or constant A titrations. Why bother with them any more?

Paper II - It is difficult for me to see the advantage in your method of plotting data. Is the method of evaluating <u>k</u> "experimental" if you have to try fitting arbitrary values to data which may be explained "with greater economy" by omitting an arbitrary <u>k</u> (or g or a)? I still think we have the advantage of you there, in an admittedly over-simplified linear relation that any immunologist can actually use. Which, of course is no reason for not trying to do better. Kendall seems to me to have done it more intelligibly and simply, at least, though perhaps no more logically than you.

Page 496 - Your point about antibody lost during washing is a good one and should be more rigorously checked than we did in comparing our 1929 and subsequent data. The differences were certainly small and the effect can scarcely be large or important, as we did check this point.

Page 497 - There are good points here.

Page 499 - This is a misquotation, as we showed the two to be identical to 0.01 mg. when anticarbohydrate alone was involved. The "incompleteness" of precipitation by soluble G requires better support than <u>that</u>. Inherently, small and mostly negligible effects would be understandable in ordinary precipitating systems.

Page 502 - Here, too, Kendall's treatment seems to have the advantage.

Page 503 - If you take out part of the A and the <u>k</u> becomes different, does that not mean the A removed and the A remaining are different? You merely say the same thing we do while denying it.

Paper III. This seems quite vague and so full of experimental contradictions to your point of view that it further weakens the whole structure.

Page 516 - 517 - Why should the constancy of g come into consideration in the G excess region? Perhaps both our '29 data and our Ba - inhibition zone calculations have some value here.

Page 518 - The recovery of A similar to the average by dissociation of precipitates would seem to indicate that different ks are not involved. Similarity of A after heterologous absorption applies only to homologous G, not heterologous G. How can one reactivity (or k) disappear from the same A? The change in flocculation rate due to heterol. pptn. is not pertinent because homol. pptn. will often do the same.

Page 520 - Another good point. Wish you'd try this out. However, even if a=2 k cannot be very high if most of this N adds to specific ppts.

Page 522 - Your theory is not applicable, because recombination does not take place when the salt excess is dialyzed out. Also the component ratios are changed by the salt excess.

I shall be glad to hear your views on these matters, in which I have a consuming interest, and I hope, if I have irritated you, that it will only spur you on to eliminate both the weaknesses in your treatment which you freely admit yourself, and those which I imagine I have found. If you can provide a complete, airtight theory of the precipitin reaction, no one will be happier than your well-wisher,

Michael Heidelberger